SUPPLEMENTAL MATERIAL

for the original article

Admission CT radiomic signatures outperform hematoma volume in predicting baseline clinical severity and functional outcome in the ATACH-2 trial intracerebral hemorrhage population

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1. Supplemental methods

Image pre-processing and radiomics feature extraction

In order to minimize the effects of data heterogeneity and differences in voxel dimensions on the radiomics extraction,[1,2] CT images and masks were resampled to an isotropic 1x1x1 mm voxel spacing using "B-spline" interpolation (fig. 2).[3-5] Interpolation to isotropic voxels ensures rotational invariance of texture features.[6] Then, we removed voxels outside the 1-200 Hounsfield unit (HU) range from ICH masks ("re-segmentation") to restrict analysis to a HU range encompassing brain tissue and ICH densities, but excluding dense parenchymal calcifications or osseous structures. Finally, original CT images were filtered to refine analysis of certain hematoma characteristics:[3] By applying high- and low-pass filters in each spatial direction, we generated eight decompositions per original image ("coif-1" wavelet transform).[7,8] An "edge-enhancement" Laplacian of Gaussian (LoG) filter with "sigma" settings of 2 mm, 4 mm and 6 mm yielded three additional derivative images per orignal.[8,9] "First-order" and "texture-matrix" radiomics feature extraction requires an image grey scale discretization step in pre-processing ("binning"),[6] which was implemented using a fixed bin width method with the width parameter set to 2 HU.[8] A complete list of radiomics features utilized in this study is provided in supplemental table 1. "Shape" features (n=14 features) were extracted from hematoma representations in the original images; "first-order" (n=18) and "texture-matrix" features (n=75) were extracted from original images and eleven derivative images per original (eight "coif-1" wavelet- and three LoG filtering-derivates). This approach yielded a total of n=1130 radiomics features per subject. We customized a Pyradiomics version 2.1.2 pipeline to facilitate pre-processing, derivative image generation, and feature extraction.[8,10] The Pyradiomics parameter file is depicted in supplemental figure 1.

Radiomics signature generation

The "radiomics signatures" were generated by linearly combining sets of robust radiomics features exhibiting strong association with admission GCS, admission NIHSS, and medium-term mRS scores, while minimizing feature multicollinearity (fig. 2). Radiomics signatures were devised in the discovery cohort, and validated in the independent validation cohort (fig. 1). All statistical analysis was performed in R version 3.6.0.[11]

The robustness of individual radiomics features to intra- and inter-rater segmentation inconsistencies was investigated in a set of n=100 patients ("multiple delineation cohort") who were randomly sampled from the discovery cohort. The hematomas in these patients were segmented a second and third time by the original reviewer and an additional reviewer, respectively.[3] Subsequently, we extracted radiomics features from all three segmentation sets and calculated intra-/interclass correlation coefficient (ICC) statistics to assess the intra-/inter-rater agreement of each radiomics feature:[3] a "two-way mixed effects, absolute agreement, single rater/measurement ICC" was utilized to quantify intra-rater agreement; and a "two-way random effects, absolute agreement, single rater/measurement ICC" was applied to assess the inter-rater agreement.[12,13] Features with an ICC 95% confidence interval lower bound ≥ 0.8 in both intra- and inter-rater assessment were considered robust. In total, 1002/1130 (88.7 %) radiomics features met this criterion and were retained for further analysis. Across all features, the mean (standard deviation, SD) intra-rater and inter-rater ICC scores were 0.94 (0.13) and 0.94 (0.11), respectively. The R "psych" package "ICC" function was applied to compute ICC statistics.[14]

Robust features were subsequently standardized by subtracting the mean and dividing by the SD derived from the discovery cohort. To reduce collinearity, we generated a radiomics feature correlation matrix using the discovery cohort and Spearman's correlation coefficient (rho) as the correlation metric (R "stats" package "cor" function).[11] From any correlated feature pair with |rho| > 0.95, the feature with higher mean absolute correlation across the discovery cohort was excluded (R "caret" package "findCorrelation" function).[15] A total of 424/1002 (42.3 %) features were retained in the collinearity-reduced feature set.

Finally, we utilized the discovery cohort and fitted least absolute shrinkage and selection operator (LASSO)-regularized ordinal logistic regression (OLR) models to generate three separate radiomics signatures associated with the target scores (i.e. GCS, NIHSS and mRS). The "ordinalNet" function (R "ordinalNet" package)[16] was configured to fit OLR models with the retained radiomics features as input variables, and the target score as the dependent variable (function arguments: family="cumulative", link="logit", parallelTerms=TRUE); OLR models were LASSO-regularized (function argument: alpha=1) and reversed (function argument: reverse=TRUE; causes radiomics signature scores and target scores to be positively correlated). After OLR model fitting, regression coefficients were extracted from the "ordinalNet" objects, and radiomics features with regression coefficients equal to zero were excluded. The linear combination of the remaining features weighted by their respective OLR coefficients was defined as the radiomics signature corresponding to given target scores. Radiomics signature scores were calculated for all subjects in the discovery and independent validation cohorts by plugging in the radiomics feature values corresponding to each individual patient. Certain target score levels were pooled prior to OLR model fitting to avoid data sparsity: all GCS levels < 9 were pooled, creating a new variable with 8 levels (range: 8-15); and each pair of adjacent NIHSS levels ≤ 25 was pooled, and all levels >25 were pooled, creating a new variable with 14 levels (range: 0-13). The "ordinalNet" "lambda"-parameter was optimized prior to OLR model fitting (R "ordinalNet" package "ordinalNetTune" function):[16] A lambda sequence of n=20 lambda values defined by "ordinalNetTune" was evaluated in 10-fold stratified cross validation with the dependent variable levels as strata. The lambda value maximizing the averaged test fold log-likelihood was utilized in OLR model fitting.

2. Supplemental tables

Supplemental table 1 List of extracted radiomics features

Feature Family		Feature name
First-order	1	10th percentile
	2	90th percentile
	3	Energy
	4	Entropy
	5	Interquartile Range
	6	Kurtosis
	7	Maximum
	8	Mean
	9	Mean Absolute Deviation
	10	Median
	11	Minimum
	12	Range
	13	Robust Mean Absolute Deviation
	14	Root Mean Squared
	15	Skewness
	16	Total Energy
	17	Uniformity
	18	Variance
Shape	1	Elongation
	2	Flatness
	3	Least Axis Length
	4	Major Axis Length
	5	Maximum 2D Diameter (Column)
	6	Maximum 2D Diameter (Row)
	7	Maximum 2D Diameter (Slice)
	8	Maximum 3D Diameter
	9	Mesh Volume
	10	Minor Axis Length
	11	Sphericity
	12	Surface Area
	13	Surface Area to Volume Ratio
	14	Voxel Volume
Texture - Gray Level Cooccurrence Matrix Features (glcm)	1	Autocorrelation
	2	Cluster Prominence
	3	Cluster Shade
	4	Cluster Tendency
	5	Contrast
	6	Correlation
	7	Difference Average
	8	Difference Entropy
	9	Difference Variance

	10	Informational Measure of Correlation 1	
	11	Informational Measure of Correlation 2	
	12	Inverse Difference	
	13	Inverse Difference Moment	
	14	Inverse Difference Moment Normalized	
	15	Inverse Difference Normalized	
	16	Inverse Variance	
	17	Joint Average	
	18	Joint Energy	
	19	Joint Entropy	
	20	Maximal Correlation Coefficient	
	21	Maximum Probability	
	22	Sum Average	
	23	Sum Entropy	
	24	Sum of Squares	
Texture - Gray Level Size Zone Matrix Features (glszm)	1	Gray Level Non-Uniformity	
	2	Gray Level Non-Uniformity Normalized	
	3	Gray Level Variance	
	4	High Gray Level Zone Emphasis	
	5	Large Area Emphasis	
	6	Large Area High Gray Level Emphasis	
	7	Large Area Low Gray Level Emphasis	
	8	Low Gray Level Zone Emphasis	
	9	Size Zone Non-Uniformity	
	10	Size Zone Non-Uniformity Normalized	
	11	Small Area Emphasis	
	12	Small Area High Gray Level Emphasis	
	13	Small Area Low Gray Level Emphasis	
	14	Zone Entropy	
	15	Zone Percentage	
	16	Zone Variance	
Texture - Gray Level Run Length Matrix Features (glrlm)	1	Gray Level Non-Uniformity	
	2	Gray Level Non-Uniformity Normalized	
	3	Gray Level Variance	
	4	High Gray Level Run Emphasis	
	5	Long Run Emphasis	
	6	Long Run High Gray Level Emphasis	
	7	Long Run Low Gray Level Emphasis	
	8	Low Gray Level Run Emphasis	
	9	Run Entropy	
	10	Run Length Non-Uniformity	
	11	Run Length Non-Uniformity Normalized	
	12	Run Percentage	
	13	Run Variance	

	14	Short Run Emphasis
	15	Short Run High Gray Level Emphasis
	16	Short Run Low Gray Level Emphasis
Texture - Neighboring Gray Tone Difference Matrix Features (ngtdm)	1	Busyness
	2	Coarseness
	3	Complexity
	4	Contrast
	5	Strength
Texture - Gray Level Dependence Matrix Features (gldm)	1	Dependence Entropy
	2	Dependence Non-Uniformity
	3	Dependence Non-Uniformity Normalized
	4	Dependence Variance
	5	Gray Level Non-Uniformity
	6	Gray Level Variance
	7	High Gray Level Emphasis
	8	Large Dependence Emphasis
	9	Large Dependence High Gray Level Emphasis
	10	Large Dependence Low Gray Level Emphasis
	11	Low Gray Level Emphasis
	12	Small Dependence Emphasis
	13	Small Dependence High Gray Level Emphasis
	14	Small Dependence Low Gray Level Emphasis

List of Pyradiomics[10] features utilized in this study. Exact feature definitions are provided in ref.[8].

Supplemental table 2 Radiomics signatures

Supplemental table 2.1 GCS radiomics signature

Feature identifier [a]				Coefficient (β) [b]
Pre-processing		Family	Feature name	
original	n/a	shape	Maximum 2D Diameter Slice	-0.25827
original	n/a	shape	Least Axis Length	-0.13572
wavelet	HHH	ngtdm	Busyness	-0.12661
original	n/a	shape	Minor Axis Length	-0.12209
wavelet	LHL	glcm	Informational Measure of Correlation 2	0.077663
wavelet	LLL	glcm	Inverse Variance	-0.02141
wavelet	LLH	glcm	Inverse Difference Moment Normalized	-0.0132

Supplemental table 2.2 NIHSS radiomics signature

Feature identifier [a]				Coefficient (β) [b]
Pre-processing		Family	Feature name	
original	n/a	shape	Maximum 2D Diameter Row	0.359905
LoG	2 mm	glszm	Gray Level Non Uniformity	0.252347
wavelet	HLL	glcm	Correlation	-0.22426
original	n/a	shape	Least Axis Length	0.186725
original	n/a	shape	Maximum 2D Diameter Column	0.177626
wavelet	HLL	firstorder	Median	0.170986
wavelet	HHL	glcm	Cluster Prominence	0.151743
LoG	6 mm	firstorder	Mean	-0.14751
LoG	6 mm	firstorder	90th Percentile	-0.14553
LoG	4 mm	ngtdm	Busyness	0.140971
wavelet	LHL	glcm	Informational Measure of Correlation 2	-0.13452
wavelet	HLL	glcm	Informational Measure of Correlation 2	-0.12087
wavelet	LLH	glszm	Zone Entropy	0.112626
wavelet	LHL	ngtdm	Strength	0.111311
LoG	2 mm	gldm	Small Dependence Low Gray Level Emphasis	-0.09674
LoG	4 mm	firstorder	90th Percentile	-0.06332
wavelet	LLL	firstorder	Robust Mean Absolute Deviation	-0.05659
wavelet	LLH	gldm	Dependence Non Uniformity Normalized	-0.02798
wavelet	HLL	glszm	Large Area Low Gray Level Emphasis	-0.02468
wavelet	HLH	ngtdm	Busyness	0.015528
wavelet	HLH	gldm	Dependence Variance	-0.01111
LoG	6 mm	ngtdm	Strength	-0.00704
wavelet	LHL	firstorder	Kurtosis	0.000792

Supplemental table 2.3 mRS radiomics signature

Feature identifier [a]				Coefficient (β) [b]
Pre-processing		Family	Feature name	
original	n/a	shape	Least Axis Length	0.261058
LoG	6 mm	glrlm	Run Variance	0.145372
original	n/a	shape	Maximum 2D Diameter Column	0.139962
wavelet	HLH	gldm	Dependence Variance	-0.06962
wavelet	LLL	glcm	Informational Measure of Correlation 1	0.069093
wavelet	LLH	glszm	Zone Entropy	0.047251
wavelet	HLL	glcm	Informational Measure of Correlation 1	0.040113
original	n/a	glcm	Informational Measure of Correlation 2	-0.00589
wavelet	HHL	glszm	Size Zone Non Uniformity	0.001499

[a] Feature identifiers are composed of a pre-processing specification (left column: type of pre-processing, i.e. wavelet- or LoG-filtering or original; right column: 3-letter directional specification of wavelet decomposition,[7,8] or LoG sigma setting[8]), and the feature family and feature name (supplemental table 1).

[b] Regression coefficient from LASSO-regularized ordinal logistic regression model. Note that radiomics features were standardized before fitting the model; hence, the reported coefficients pertain to standardized radiomics features.

LASSO-regularized ordinal logistic regression models were fitted to the discovery cohort to generate three separate radiomics signatures associated with the target scores (i.e. GCS, NIHSS and mRS). After fitting the model, regression coefficients were extracted and radiomics features with regression coefficients equal to zero were excluded. The linear combination of the remaining features weighted by their respective coefficients was defined as the radiomics signature corresponding to each target variable.

Supplemental table 3 Multiple ordinal logistic regression analysis of 3-month mRS score (adjusted for ICH volume and hematoma expansion)

Coefficient (β) [a]		Standard error	t-value	p-value
Discovery cohort (n=433 with hematoma expansion variable available)				
GCS	0.13	0.06	2.24	p = 0.02
NIHSS	0.16	0.02	7.09	p < 0.001
ICH volume	-0.30	0.18	-1.64	p = 0.10
Presence of intraventricular hemorrhage	0.91	0.22	4.18	p < 0.001
Age	0.06	0.01	7.38	p < 0.001
Hematoma expansion	0.23	0.21	1.14	p = 0.25
mRS radiomics signature	1.50	0.36	4.17	p < 0.001
Independent validation cohort (n=435 with hematoma expansion variable available)				
GCS	0.14	0.06	2.33	p = 0.02
NIHSS	0.15	0.02	7.37	p < 0.001
ICH volume	0.13	0.21	0.62	p = 0.53
Presence of intraventricular hemorrhage	0.95	0.21	4.43	p < 0.001
Age	0.04	0.01	5.68	p < 0.001
Hematoma expansion	1.00	0.21	4.84	p < 0.001
mRS radiomics signature	0.76	0.33	2.29	p = 0.02

[a] Regression coefficients from multiple ordinal logistic regression analysis of 3-month mRS score. Note that the ICH volume variable was standardized before fitting the model.

Supplemental table 4 Intersections of radiomics signatures

∩	GCS signature	NIHSS signature	mRS signature
GCS signature	n=7 features	• original_shape_Least Axis Length • wavelet_LHL_glcm_Informational Measure of Correlation 2	• original_shape_Least Axis Length
NIHSS signature	• original_shape_Least Axis Length • wavelet_LHL_glcm_Informational Measure of Correlation 2	n=23 features	• original_shape_Least Axis Length • original_shape_Maximum 2D Diameter Column • wavelet_LLH_glszm_Zone Entropy • wavelet_HLH_gldm_Dependence Variance
mRS signature	• original_shape_Least Axis Length	• original_shape_Least Axis Length • original_shape_Maximum 2D Diameter Column • wavelet_LLH_glszm_Zone Entropy • wavelet_HLH_gldm_Dependence Variance	n=9 features

Features in the intersections of radiomics signatures. Refer to supplemental table 2 for a complete list of features included in each signature.

Supplemental table 5 Visual ICH markers

Visual ICH marker [a]	Discovery cohort (subsample of n = 200 patients)	Independent validation cohort (subsample of n = 200 patients)	p value discovery vs. independent
Blend sign – n (%)			
Present	23 (11.5 %)	22 (11.0 %)	0.87
Absent	177 (88.5 %)	178 (89.0 %)	
Hypodensity – n (%)			
Present	147 (73.5 %)	147 (73.5 %)	1.00
Absent	53 (26.5 %)	53 (26.5 %)	
Swirl sign – n (%)			
Present	19 (9.5 %)	14 (7.0 %)	0.36
Absent	181 (90.5 %)	186 (93.0 %)	
Black hole sign – n (%)			
Present	16 (8.0 %)	22 (11.0 %)	0.31
Absent	184 (92.0 %)	178 (89.0 %)	
Island sign – n (%)			
Present	8 (4.0 %)	7 (3.5 %)	0.79
Absent	192 (96.0 %)	193 (96.5 %)	
Satellite sign – n (%)			
Present	34 (17.0 %)	35 (17.5 %)	0.89
Absent	166 (83.0 %)	165 (82.5 %)	
Fluid level – n (%)			
Present	1 (0.5 %)	1 (0.5 %)	1.00
Absent	199 (99.5 %)	199 (99.5 %)	
Irregular shape – n (%)			
Present	82 (41.0 %)	68 (34.0 %)	0.15
Absent	118 (59.0 %)	132 (66.0 %)	

[a] Three independent readers visually identified non-contrast CT markers of ICH, and the majority vote across their reads is depicted. The diagnostic criteria for visual markers were adopted from Morotti et al.[17]

Supplemental table 6 Visual ICH marker signatures

Supplemental table 6.1 GCS visual ICH marker signature

Visual ICH marker [a]	Coefficient (β) [b]
Irregular shape	-0.43950
Hypodensity	-0.02996

Supplemental table 6.2 NIHSS visual ICH marker signature

Visual ICH marker [a]	Coefficient (β) [b]
Irregular shape	1.27712
Hypodensity	0.45731

Supplemental table 6.3 mRS visual ICH marker signature

Visual ICH marker [a]	Coefficient (β) [b]
Irregular shape	1.08068
Hypodensity	0.23597

[a] Three independent readers visually identified non-contrast CT markers of ICH, and the majority vote across their reads was used for this analysis. The diagnostic criteria for visual markers were adopted from Morotti et al.[17]

[b] Regression coefficient from LASSO-regularized ordinal logistic regression model.

LASSO-regularized ordinal logistic regression models were fitted to a subset of n=200 patients randomly sampled from the discovery cohort to generate three separate visual marker signatures associated with the target scores (i.e. GCS, NIHSS and mRS). After fitting the model, regression coefficients were extracted and markers with regression coefficients equal to zero were excluded. The linear combination of the remaining markers weighted by their respective coefficients was defined as the visual marker signature corresponding to each target variable.

Supplemental table 7 Correlation of visual ICH marker signature scores, radiomics signature scores and ICH volume with GCS, NIHSS and mRS scores

	Discovery cohort (subsample of n=200 patients)		Independent validation cohort (subsample of n=200 patients)	
GCS	**Rho** [a]	**Comparison of correlations** [b]	**Rho** [a]	**Comparison of correlations** [b]
ICH volume*(-1) [c]	0.44 (p < 0.001)	p = 0.048 (ICH vol vs Visual); p = 0.03 (ICH vol vs Radiomics)	0.40 (p < 0.001)	p = 0.08; p = 0.08
Visual ICH marker signature	0.31 (p < 0.001)		0.30 (p < 0.001)	
Radiomics signature	0.46 (p < 0.001)		0.43 (p < 0.001)	
NIHSS	**Rho** [a]	**Comparison of correlations** [b]	**Rho** [a]	**Comparison of correlations** [b]
ICH volume	0.62 (p < 0.001)	p = 0.10; p < 0.001	0.50 (p < 0.001)	p = 0.15; p = 0.004
Visual ICH marker signature	0.54 (p < 0.001)		0.42 (p < 0.001)	
Radiomics signature	0.73 (p < 0.001)		0.60 (p < 0.001)	
mRS	**Rho** [a]	**Comparison of correlations** [b]	**Rho** [a]	**Comparison of correlations** [b]
ICH volume	0.35 (p < 0.001)	p = 0.12; p < 0.001	0.28 (p < 0.001)	p = 0.36; p < 0.001
Visual ICH marker signature	0.44 (p < 0.001)		0.34 (p < 0.001)	
Radiomics signature	0.43 (p < 0.001)		0.40 (p < 0.001)	

[a] Spearman's rho

[b] R.R. Wilcox' percentile bootstrap method for comparing dependent robust correlations [18]

[c] To obtain a positive rho, the ICH volume variable was negated prior to calculating its correlation with GCS score

3. Supplemental figures

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Supplemental figure 1 The Pyradiomics parameter file

4. Supplemental References

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